PATENT SPECIFICATION (11) 1 361 289

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(21) Application No. 27693/71 (22) Filed 14 June 1971 (19)

(44) Complete Specification published 24 July 1974

(51) International Classification A61M 37/00

(52) Index at acceptance
A5R 71 83U

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(54) BANDAGE FOR ADMINISTERING DRUGS

(71) We, ALZA CORPORATION, 950 Page Mill Road, Palo Alto, California, United States of America, a Corporation organized and existing under the laws of the State of California, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a bandage for use in the continuous administration of systemically active drugs.

One primary objective of drug therapy is to achieve a particular blood level or concentartion of drug in the blood circulation for a period of time. Many drugs, such as the steroidal hormones, are absorbed in a relatively short period of time, and are not long acting due to rapid metabolism and excretion following administration. To obtain the desired therapeutic effect, it is necessary in most cases to establish a dosage regime of multiple unit doses over a 24 hour period. Most drugs are administered orally or by injection and neither of these modes of administration achieves the desired blood level of drug in the circulation in the typical case.

With oral administration of drugs, it is difficult if not impossible to achieve a constant blood level of drug in the circulation. This is true even though the drug is administered at periodic intervals according to a well defined schedule. One reason for this is that the rate of absorption of drugs through the gastrointestinal tract is affected by the contents of the tract. Such variables as whether the drug is administered before or after eating and the type and quantity of food eaten (for example, high or low fat content) or administered before or after a bowel movement, can control the rate of absorption of the drugs. Since absorption of the drugs takes place in the small intestine, the time of passage through the small intestine is another governing factor. This in turn is affected by the rate of peristaltic contracting, adding further uncertainty. Also important is the rate of circulation of blood to the small intestine.

The almost inevitable result of oral administration of drugs through the gastrointestinal tract is that the level of drug in circulation surges to a high each time the drug is administered, followed by a decline in concentration in the blood and body compartments. Thus, a plot of the concentration of drug in the circulation following a dosage schedule of several tablets a day has the appearance of a series of peaks, which may surpass the toxic threshold, and valleys. Each time the blood level decreases below a critical point needed to achieve the desired therapeutic effect that effect will no longer be obtained. Worse still, with antimicrobial drugs, the disease producing micro-organisms rapidly multiply when the concentration of drug in circulation descends below a critical point. It is likely that the drug-resistant mutant strains which are becoming increasingly prevalent and represent one of the major problems in the therapeutics of infectious diseases are formed at such times.

One approach to this problem has been the advent of the so-called sustained release or time-capsule in oral dosage form. While many of these perform satisfactorily *in vitro* and in animal or clinical studies under controlled conditions of nutrition and activity, there is little or no evidence that these dosage forms are effective for achieving a continuous and predictable level of drug in circulation over a prolonged period of time under the normal conditions encountered by the out-patient.

Many effective therapeutic agents are destroyed by microbial flora or gastro-intestinal secretions or are poorly absorbed in the gastrointestinal tract.

Administration of drugs by injection is inconvenient, and the risk of local tissue reaction and of infection is serious. Moreover, the typical result of administration by injection is a surge in blood level concentra-

tion of the drug immediately after injection, followed by a decline and another surge in concentration upon subsequent injections.

Other dosage forms such as rectal suppositories and sublingual lozenges also produce non-uniform levels of the therapeutic agent in circulation. These dosage forms require great patient cooperation, have low patient acceptability, and are sparingly used throughout most of the world.

Dosage forms described above all bring about a pulse entry of drug, that is, a concentrated dose of drug is brought into contact with an organ of entry at a particular time unit. Undoubtedly, this creates drug concentrations beyond the capacity of the active centers to accept (that is, the saturation point is exceeded by many orders of magnitude) and, also, until dilution in body fluids takes place, may exceed the capacity of metabolic and excretory mechanisms. The result is that a toxic level of drug is allowed to build up for a period of time, with detrimental effects for particular tissues or organs. To obtain persistence of effect, the usual industrial approach is to make the initial dose high or to modify the drug structure to obtain a longer metabolic half-life of the drug in the circulation. Raising the initial dosage only worsens the problem. Many derivatives with long half-lives have a lower therapeutic index (i.e. ratio between the median toxic dose and the median effective dose) than that of the parent compounds; and therefore these approaches are not the answer to the problem.

To avoid the problems discussed above, it has been suggested that systemically active drugs can be administered through the skin. Percutaneous administration can have the advantage of permitting continuous administration of drug to circulation over a prolonged period of time to obtain a uniform delivery rate and blood level of drug. Commencement and termination of drug therapy are initiated by the application and removal of the dosing device from the skin. Uncertainties of administration through the gastrointestinal tract and the inconvenience of administration by injection are eliminated. Since a high concentration of drug never enters the body, problems of pulse entry are overcome and metabolic half-life is not a factor of controlling importance.

Despite these advantages of administering systemically active drugs through the skin, prior devices designed for this purpose were either impractical or inoperative and did not provide continuous administration and delivery rate. This form of administration has not been accepted by the medical profession and the only prior art manner of obtaining continuous delivery rate remains the continuous intravenous drip.

Accordingly, an object of this invention is to provide a device for the administration of systematically active drugs which overcomes the aforesaid disadvantages inherent in prior art modes of administration.

Another object of this invention is to provide a reliable and easily applied device for continuously administering controlled quantities of systemically active drugs through the skin.

Still another object of this invention is to provide a device for administering systemically active drugs through the oral mucosa.

A further object of this invention is to provide a complete dosage regime for a particular time period, the use of which requires patient intervention only for initiation and termination.

According to the present invention there is provided a medical bandage for use in the continuous administration to the circulation of a systemically active drug over a prolonged period of time by absorption through the external body skin or mucosa, said bandage comprising a backing which is impervious to the drug and defines one face of the bandage; a pressure-sensitive adhesive for contact with the skin or mucosa of a patient, the external surface thereof defining at least part of the other face of the bandage; and disposed between said faces at least one reservoir of a systemically active drug having a wall member formed of a material permeable by the drug at a sustained and predetermined rate.

One embodiment of this invention resides in a bandage comprised of a backing member bearing a pressure-sensitive adhesive layer on one surface thereof. The pressure-sensitive adhesive has distributed therethrough a plurality of discrete reservoirs of microcapsule size acting as said at least one drug reservoir. These discrete reservoirs may each be comprised of a systemically active drug encapsulated within the said drug-permeable material. Alternatively, they may each be comprised of a matrix of the drug-permeable material, said matrix having the systemically active drug distributer therethrough.

In another embodiment of this invention, the at least one reservoir comprises a reservoir layer containing the systemically active drug and discrete from the pressure-sensitive adhesive.

In another aspect of the immediately foregoing embodiment of the invention, the bandage includes a membrane interposed between the reservoir layer and the pressure-sensitive adhesive, said membrane being formed of a material permeable by the drug at a sustained and predetermined rate.

Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description of

the invention which follows, and from the drawings.

In the drawings:

Fig. 1 is a perspective view of one bandage of the invention.

Fig. 2 is a cross-sectional view of the bandage illustrated in Fig. 1.

Fig. 3 is a perspective view of another bandage of the invention.

Fig. 4 is a cross-sectional view of the bandage illustrated in Fig. 3.

Fig. 5 is a cross-sectional view of a modified bandage of the invention including a solubility membrane between the reservoir and the pressure sensitive adhesive.

As illustrated in Figs. 1 and 2, the bandage 10 of this invention is comprised of a backing member 11 bearing a pressure-sensitive adhesive layer 14 on one surface thereof. The adhesive layer 14 has microcapsules 18 (not shown in Fig. 1) of a systemically active drug encapsulated with a material permeable to passage of the drug uniformly distributed therethrough.

As illustrated in Figures 3 and 4, an alternative design of a bandage 10 in accordance with this invention comprises a backing member 11 having a reservoir 12 on one surface thereof. The wall 13 of the reservoir 12 distant from the backing member 11 bears a pressure-sensitive adhesive layer 14. The reservoir 12 contains a systemically active drug 15 and at least wall 13 of the reservoir 12 in contact with the adhesive layer 14 is permeable to passage of the drug.

Figure 5 illustrates a modified form of the bandage shown in Figures 3 and 4, in which a membrane 16 is interposed between the reservoir 12 and the pressure-sensitive adhesive layer 14.

To use the bandage 10 of the invention, it is applied to the patient's skin. The adhesive layer 14 should be in firm contact with the skin, forming a tight seal therewith. The drug within the microcapsules 18 or the reservoir layer 12, whether in solid form or solution, migrates through the walls of the microcapsules or the reservoir layer and into adhesive layer 14, as by diffusion. Ordinarily, one would expect the drug migration to cease when sufficient drug has reached the outer surface of the microcapsules 18 or the reservoir layer 12 to create an equilibrium or when the adhesive layer 14 has become saturated with the drug. However, when the adhesive layer 14 is in contact with the patient's skin, drug molecules which are continuously removed from the outer surface of the microcapsules 18 or the reservoir layer 12 migrate through the adhesive to the outer surface of the adhesive layer and are absorbed by the skin. Absorbed drug molecules pass through the skin and enter the circulation through the capillary network. While the bandage may be applied to any area of the patient's skin, the lower back and buttocks are the areas of choice. In like manner, the bandage can be applied to the mucosa of the mouth, for example, by application to the palate or the buccal mucosa, to obtain absorption of the drug by the oral mucosa. Although obtaining a liquid-tight adhesive seal between the skin and bandage is important; it becomes critical in the mouth. Without such a seal, irrigation of the oral mucosa by saliva will transfer the drug to the gastrointestinal tract, rather than to circulation through the oral mucosa.

Those skilled in the art will appreciate that the bandage of this invention significantly differs from prior art wound dressings or bandages containing antiseptics or topically active drugs. The bandage of this invention contains a systemically active drug within a reservoir and is applied to unbroken skin, to introduce the drug to circulation in the blood stream and produce a pharmacologic response at a site remote from the point of application of the bandage. Thus, the bandage functions as an external drug reservoir and provides a complete dosage regime for a particular time period.

The term "reservoir" as used in a general sense herein to define the drug-containing portion of the bandages is intended to connote a broad class of structures capable of fulfilling the intended function and includes both discrete microcapsules or the like as well as distinct reservoir compartments or layers. Likewise, the foregoing term encompasses walled containers having one or more interior drug-containing chambers as well as solid matrixes having a systemically active drug distributed therethrough. In the case of a drug distributed throughout a solid matrix, said matrix itself can constitute the wall member of the reservoir.

In practicing this invention, one can employ any systemically active drug which will be absorbed by the body surface to which the bandage is applied. The term "systemically active drug" is used herein in its broadest sense as indicating a substance or composition which will give a pharmacologic response at a site remote from the point of application of the bandage. Of course, the amount of drug necessary to obtain the desired therapeutic effect will vary depending on the particular drug used. Suitable drugs include, without limitation, Anti-microbial agents such as penicillin, tetracycline, oxytetracycline, chlortetracycline, chloramphenicol, and sulfonamides; Sedatives and Hypnotics such as pentabarbital sodium, phenobarbital, secobarbital sodium, codeine, (α-bromoisovaleryl) urea, carbromal, and sodium phenobarbital; Psychic Energizers such as 3-(2-aminopropyl) indole acetate and 3-(2-aminobutyl) indole acetate; Tranquilizers such as resperine, chlorpromazine hy-

drochloride, and thiopropazate hydrochloride; Hormones such as adrenocorticosteroids, for example, 6α-methylprednisolone, cortisone, cortisol, and triamcinolone; androgenic steroids, for example, methyltestosterone, and fluoxymesterone; estrogenic steroids, for example, estrone, 17β-estradiol and ethinyl estradiol; progestational steroids, for example, 17α-hydroxyprogesterone acetate, medroxyprogesterone acetate, 19-norprogestcrone, and norethindrone; and thyroxine, Antipyretics such as aspirin, salicylamide, and sodium salicylate; Antispasmodics such as atropine, methscopolamine bromide, methscopolamine bromide with phenobarbital; Anti-malarials such as the 4-aminoquinolines, 8-aminoquinolines, and pyrimethamine; and Nutritional agents such as vitamins, essential amino acids, and essential fats.

Drugs which alone do not pass through the skin or oral mucosa can be dissolved in an absorbable, pharmacologically acceptable solvent to achieve passage through the external body layer. Suitable solvents include alcohols containing 2 to 10 carbon atoms, such as hexanol, cyclohexanol, benzylalcohol, 1,2-butanediol, glycerol, and amyl alcohol; hydrocarbons having 5 to 12 carbon atoms such as n-hexane cyclohexane, and ethyl benzene, aldehydes and ketones having 4 to 10 carbon atoms such as heptyl aldehyde, cyclohexanone, and benzaldehyde; esters having 4 to 10 carbon atoms such as amyl acetate and benzyl propionate; etheral oils such as oil of eucalyptus, oil of rue, cumin oil, limonene, thymol, and 1-pinene; halogenated hydrocarbons having 2 to 8 carbon atoms such as n-hexyl chloride, n-hexyl bromide, and cyclohexyl chloride; or mixtures of any of the foregoing solvents. Also, with drugs which do not pass through the skin or oral mucosa, simple pharmacologically acceptable derivatives of the drugs, such as ethers, esters, amides, acetals, etc. having the desired absorption property can be prepared and used in practicing the invention. Of course, the derivatives should be such as to convert to the active drugs within the body through the action of body-enzyme-assisted transformations, pH, etc.

The reservoir containing the drug is formed of a material permeable to the drug, to permit passage of the drug, as by diffusion, through the reservoir wall at a relatively low rate. Normally, the rate of passage of the drug through the reservoir wall is dependent on, for example, the solubility of the drug or drug solution therein, as well as on the reservoir wall thickness. This means that selection of appropriate materials for fabricating the reservoir wall will be dependent on the particular drug to be used in the bandage. By varying the composition and thickness of the reservoir wall, the dosage rate per area of bandage can be controlled, for the reservoir wall acts to meter the flow or diffusion of drug from the reservoir to the adhesive layer. Thus, bandages of the same surface area can provide different dosages of a drug by varying the characteristics of the reservoir wall. While it is only necessary that the wall of the reservoir in contact with the pressure-sensitive adhesive on the skin be permeable to the drug, for convenience, all of the walls of the reservoir normally are formed of the same material. This, of course, is always true in the case of microcapsule or matrix reservoirs.

Materials used to form the reservoir are those capable of forming film walls or matrixes through which drug can pass by diffusion. Fabrics, fibrous masses, and the like, which merely absorb and release drug solutions in a gross and uncontrollable manner, are unsuitable since predictable drug release cannot be obtained.

One presently preferred class of materials for use in forming the drug reservoir are the organopolysiloxane rubbers, commonly known as silicone rubbers. Such silicone rubbers are the conventional heat-curable silicone rubbers and the room temperature vulcanizable silicone rubbers.

Conventional silicone rubbers which are converted to the rubbery state by the action of heat are predominantly linear organopolysiloxanes having an average degree of substitution of about two organic groups attached directly to silicon per silicon atom. Preferably, the organic groups are monovalent hydrocarbon radicals such as alkyl, aryl, alkenyl, alkaryl, aralkyl, and of these, the methyl, phenyl and vinyl radicals are most preferred.

Variation of the organic groups in the silicone rubber can be used to vary the solubility of the drug in the polymer and hence can control the sped of migration of the drug through the polymer. Also, drugs which are insoluble in one type of silicone rubber may be soluble in a different type of polymer. One especially preferred class of silicone polymers are the pure dimethylpolysiloxanes.

Room temperature vulcanizable silicone rubbers are also commercially available and are known to the art. In general, they employ the same silicone polymers as discussed above although the polymers often contain a greater amount of silicon bonded hydroxy groups. This type of silicone rubber will cure at room temperature in the presence of an appropriate catalyst, such as stannous 2-ethylhexoate.

Exemplary patents disclosing the preparation of silicone rubbers are U.S. Patents Nos. 2,541,137; 2,723,966; 2,863,846; 2,890,188; 2,927,907; 3,002,951; and 3,035,016.

Another class of materials suitable for use in forming the reservoir are the hydrophilic polymers of monoesters of an olefinic acid, such as acrylic acid and methacrylic acid. Exemplary polymers of this class include poly (hydroxyethylacrylate) and poly (hydroxyethylmethacrylate). These polymers are commercially available and their preparation is described in U.S. Patents Nos. 2,976,576 and 3,220,960, as well as in Belgian Patent No. 701,813. When using these hydrophilic polymers, the drug is normally dissolved in a solvent such as a lower alcohol to promote passage of the drug through the polymer.

Other exemplary materials for use in forming the reservoir of this invention include polyvinylalcohol, polyvinylacetate, plasticized polyvinylchloride, plasticized nylon, collagen, modified collagen, gelatin, and waxes such as polyethylene wax, oxidized polyethylene wax, hydrogenated castor oil, etc.

In the embodiment illustrated in Figs. 1 and 2, microcapsules constitute the drug reservoir. To provide the microcapsules, particles or solutions of drugs can be encapsulated with thin coatings of the encapsulating material to form microcapsules. Alternatively, the encapsulating material can be uniformly impregnated with the drug or drug solution to form microcapsules which are a matrix having the drug distributed therethrough. If desired, particles of a matrix, such as starch, gum acacia, gum tragacanth, and polyvinylchloride, can be impregnated with the drug and encapsulated with another material such as the encapsulating materials previously discussed which function as a membrane to meter the flow of drug to the adhesives; use of a matrix and a separate membrane of drug-permeable material can slow the passage of the drug from the matrix which is desirable with drugs that are released too rapidly from available matrix materials. In contrast, by encapsulating a solution of the drug, the solvent speeds passage of the drug through the microcapsule walls.

Any of the encapsulation or impregnation techniques known in the art can be used to prepare the microcapsules or matrix reservoirs to be incorporated into the adhesive base in accord with this invention. Thus, the drug or drug solution can be added to the matrix material in liquid form and uniformly distributed therethrough by mixing; or solid matrix material can be impregnated with the drug by immersion in a bath of the drug to cause the drug to diffuse into the material. Subsequently, the solid material can be reduced to fine microcapsule-like reservoirs by grinding. Alternatively, fine particles or solutions of the drug can be encapsulated with a coating. One suitable technique comprises suspending dry particles of the drug in an air stream and contacting that stream with a stream containing the encapsulating material to coat the drug particles. Usually, the microcapsules or like matrix reservoirs have an average particle size of from 1 to 1000 microns, although this is not critical to the invention.

The microcapsules or like matrix reservoirs, however made, are then mixed with a pressure-sensitive adhesive. The mixture is then coated onto a backing member, usually to provide an adhesive layer 0.01 to 7 millimeters thick, although these limits can be exceeded if more or less drug is required. The purpose of the backing is to provide support for the bandage and to prevent passage of the drug through the adhesive surface away from the body surface to which the bandage is applied.

In the embodiment employing a distinct reservoir layer, the reservoir can be formed by molding into the form of a hollow container with the drug trapped therein. Alternatively, the reservoir can be in the form of an envelope formed from sheets of polymeric material permeable to passage of the drug and enclosing the drug. While the walls of the reservoir can be of any convenient thickness, usually they have a thickness of from 0.01 to 7 millimeters. In a further embodiment, the reservoir can comprise a solid matrix having the drug uniformly distributed therethrough. This can be accomplished by adding the drug to the matrix material in liquid form and subsequently converting the matrix to a solid by curing or cooling; or by immersing the solid matrix in the drug to effect diffusion of the drug into the matrix. Thus, the reservoir of the bandage of this invention can be a hollow drug container or a solid or gel matrix. The drug permeates the reservoir wall to the adhesive layer or skin, with the rate controlled by the composition and thickness of the reservoir wall.

One face of the drug reservoir usually bears a separate backing member. The purpose of the backing member is to prevent passage of the drug through the surface of the reservoir distant from the adhesive layer. An ancillary purpose of the backing member is to provide support for the bandage, where needed. When the outer surface of the reservoir is impermeable to the drug and strong enough, that surface can constitute the backing of the bandage, a separate backing member being unnecessary. The other surface of the reservoir can bear a coating of a pressure-sensitive adhesive.

In a modified embodiment of the reservoir layer embodiment, passage of the drug from the reservoir to the adhesive or skin is further controlled by interposing a membrane therebetween. This membrane, as with the

walls of the reservoir, is formed of a material permeable to the drug at a sustained and predetermined rate. Any of the materials previously mentioned for use in fabricating the walls of the reservoir may be used as for this membrane. Alternatively, the membrane will have different characteristics than the reservoir wall of the particular device. This use of the reservoir wall and the membrane, allows for precise control of drug release; for the thickness and composition of both can be varied to provide for a wide range of dosage levels per given area of bandage.

Backing members for any of the bandages of the invention can be flexible or non-flexible and suitable materials include Cellophane ("Cellophane" is a Trade Mark), cellulose acetate, ethyl cellulose, plasticized vinyl acetate-vinyl chloride copolymers, polyethylene terephthalate, nylon, polyethylene, polyvinylidine chloride, coated flexible fibrous backings such as paper and cloth, and aluminum foil.

Any of the well known dermatologically acceptable pressure-sensitive adhesives which permit drug migration can be used in practising this invention. Exemplary adhesives include acrylic resin such as polymers of esters of acrylic acid with alcohols such as n-butanol, n-pentanol, isopentanol, 2-methyl butanol, 1-methyl butanol, 1-methyl pentanol, 2-methyl pentanol, 3-methyl pentanol, 2-ethyl butanol, isooctanol, n-decanol, or n-dodecanol, alone or copolymerized with ethylenically unsaturated monomers such as acrylic acid, methacrylic acid, acrylamide, methacrylamide, N-alkoxymethyl acrylamides, N-alkoxymethylmethacrylamides, N-tert. butylacrylamide, itaconic acid, vinylacetate, N-branched alkyl maleamic acids wherein the alkyl group has 10 to 24 carbon atoms, glycol diacryates, or mixtures of these; elastomeric silicone polymers; polyurethane elastomers; rubbery polymers, such as polyisobutylene, polyisoprene, and polybutadiene; vinyl polymers, such as polyvinylalcohol, polyvinyl pyrrolidone, and polyvinylacetate; cellulose derivatives such as ethyl cellulose, methyl cellulose, and carboxymethyl cellulose; natural gums such as guar, acacia, pectins, etc. For use in contact with the oral mucosa rubbery polymers such as polyisobutylene, with or without gum modifiers gives good results, as do polyvinyl alcohol, polyvinyl pyrrolidone, cellulose derivatives and other. The adhesives may be compounded with tackifiers and stabilizers as is well known in the art.

The required surface area of the bandage will depend on the activity of the drug and the rate of its absorption through the skin and the part of the patient's body to which it is to be attached. Usually, the adhesive face of the bandage has a surface area of 0.5 to 400 square centimeters, although smaller or larger area bandages can be used.

It will of course be appreciated that the pressure sensitive adhesive surface need not form a continuous layer on the bandages. Particularly in the case of a bandage having a distinct reservoir layer, equally advantageous results are obtained by providing an annular surface of adhesive around the periphery of the bandage face. In this manner a liquid-tight adhesive seal between the bandage and the patient's skin is maintained, and at the same time, the drug may be directly absorbed by the skin from the exposed surface of the drug reservoir layer without first migrating through an adhesive layer.

It will be appreciated that on confining the drug within a reservoir of a material, such as silicone rubber, the drug immediately begins to migrate into and through the wall member. On mixing the microcapsules or the like with the adhesive or coating the reservoir layer with adhesive, the drug passing through the walls of the microcapsules or the like or reservoir layer will enter the adhesive, eventually saturating the adhesive with the drug. To prevent passage of the drug away from the exposed surface of the adhesive prior to use, the adhesive surface of the bandage generally is covered prior to use with a protective release member, especially film or foil, such as waxed paper. Alternatively, the exposed rear surface of the backing member can be coated with a material of low-adhesion for the pressure-sensitive adhesive so that the bandage can be rolled about itself.

As a further alternative, in the embodiment of the invention employing a distinct reservoir layer, to prevent passage of the drug into the adhesive layer prior to use, the adhesive can be supplied separately from the reservoir and backing, with the device assembled at the point of use. For example, the adhesive in sheet form can have both surfaces protected with a release film and the wall of the reservoir can be similarly protected. At the point of use, the release films can be removed from the reservoir and one surface of the adhesive, the adhesive sheet applied to the reservoir wall to complete assemblage of the bandage, the remaining release film then removed from the adhesive, and the bandage then applied to the patient.

The following Examples will serve to illustrate the invention without in any way being limiting thereon.

EXAMPLE I

100 grams of 2-hydroxyethyl methacrylate is mixed with 100 grams of water and tertiary butyl peroxide (0.2 gram) is added. Ethylene glycol dimethacrylate (0.2 gram) is

added to the mixture and is heated to 70°C. The resultant, friable, polymeric foam is dried and ground to a powder to obtain average particle size of about 20 micron.

A 10 gram portion of the polymeric powder is mixed with 1 gram glyceryl trinitrate dissolved in ethyl alcohol and the resultant mixture placed on a mechanical roller until the polymeric powder has absorbed the glyceryl trinitrate to saturation. The solution is then filtered.

The resulting microcapsule-like matrix reservoirs of glyceryl trinitrate are mixed with 100 grams of a 22% solution in heptane-ethylacetate (70:30) of a viscoelastic copolymer of iso-octyl acrylate and acrylic acid (94:6) adhesive to uniformly distribute the reservoirs throughout the adhesive solution. The resulting slurry is coated onto a Cellophane sheet, 10 centimeters in width by 100 centimeters in length, and the solvent is removed by evaporation.

When applied to the skin of a subject, a 5 cm × 5 cm portion of the resulting bandage is effective to administer nitroglycerin through the skin to the circulation to provide a continuous administration of a daily dose of nitroglycerin for coronary vasodilation. If desired, the amount of the nitroglycerin to be administered may be increased or decreased by merely varying the size of the above described bandage for application to the skin.

EXAMPLE II

Liquid dimethyl silicone rubber [100 grams, Dow-Corning Silastic (Silastic is a Trade Mark)] is mixed with finely divided crystalline megesterol acetate (5 grams). After uniformly mixing the hormone with the unvulcanized silicone rubber, 0.5 gram of stannous octoate catalyst are added and the rubber cured at room temperature. The resulting silicone rubber body is reduced to microcapsule-like reservoirs of an average particle size of 100 microns.

5 grams of the resulting encapsulated megesterol acetate are mixed with an elastomeric silicone pressure-sensitive adhesive (10 grams) to uniformly distribute the microcapsule-like reservoirs throughout the adhesive. Immediately thereafter, the adhesive mixture is coated onto one surface of a 100 square centimeter Mylar ("Mylar" is a Trade Mark) sheet. The resulting bandage is used for fertility regulation.

EXAMPLE III

Dry crystalline powdered megesterol acetate (0.3 gram) is placed on a sheet of dimethyl silicone rubber having a thickness of 0.13 millimeters. The sheet is folded to provide a surface area of 100 square centimeters on each face and the flaps sealed with silicone adhesive to provide a thin envelope containing the hormone. One face surface of the envelope is bonded to a sheet of Cellophane while the other is coated with dimethyl silicone rubber adhesive to a thickness of 2 millimetres. The adhesive face surface of the completed bandage has an area of 100 square centimeters. The bandage is effective to slowly release megesterol acetate and, when applied to the female skin, is useful for fertility control.

Thus, this invention provides an easy to use device for administering systemically active drugs through the skin and oral mucosa. Uncertainties of administration through the gastrointestinal tract are avoided and a constant level of drug in the circulation can be obtained. Treatment is begun by applying the bandage to the skin or oral mucosa and terminated by removing it therefrom. The bandage can contain and administer the complete dosage requirements for a particular time period, for example, 24 hours. Intervention by the patient is required only to apply and remove the bandage, so that uncertainties are eliminated.

WHAT WE CLAIM IS:—

1. A medical bandage for use in the continuous administration to the circulation of a controlled quantity of a systemically active drug over a prolonged period of time by absorption through the external body skin or mucosa, said bandage comprising a backing which is impervious to the drug and defines one face of the bandage; a pressure-sensitive adhesive for contact with the skin or mucosa of a patient, the external surface of said pressure-sensitive adhesive defining at least part of the other face of the bandage; and disposed between said faces at least one reservoir of a systemically active drug having a wall member formed of a material permeable by the drug at a sustained and predetermined rate.

2. A bandage as claimed in Claim 1, wherein said at least one reservoir comprises a reservoir layer discrete from the pressure-sensitive adhesive.

3. A bandage as claimed in Claim 2, wherein the reservoir layer is comprised of a walled container formed at least partially from the drug-permeable material and having an interior chamber containing the

4. A bandage as claimed in Claim 3, wherein only that portion of the walled container which is to be brought contiguous with the pressure-sensitive adhesive or the skin or mucosa is formed from the drug-permeable material.

5. A bandage as claimed in Claim 2, wherein the reservoir layer is comprised of a matrix of the drug-permeable material, said matrix having the systemically active drug distributed therethrough.

6. A bandage as claimed in any of

Claims 2 to 5 further comprising a membrane interposed between said reservoir layer and said other face, said membrane being formed of a material permeable by the drug at a sustained and predetermined rate.

7. A bandage as claimed in any one of Claims 2 to 6 wherein one outer surface of the reservoir layer is impervious to the drug and constitutes the said backing member.

8. A bandage as claimed in Claim 1, comprised of a backing member bearing a pressure-sensitive adhesive layer on one surface thereof and wherein said at least one reservoir comprises a plurality of discrete reservoirs of microcapsule size distributed throughout the said pressure-sensitive adhesive layer.

9. A bandage as claimed in Claim 8, wherein each of said reservoirs is a microcapsule comprised of systemically active drug encapsulated within the said drug-permeable material.

10. A bandage as claimed in Claim 8, wherein each of said reservoirs is comprised of a matrix of the drug-permeable material, said matrix having the systemically active drug distributed therethrough.

11. A bandage as claimed in any one of Claims 8 to 10 wherein said reservoirs have an average particle size of from about 1 to 1,000 microns.

10. A bandage as claimed in any one of the preceding claims, wherein the adhesive face of the bandage has an area of from about 0.5 to 400 square centimeters.

13. A bandage as claimed in any one of the preceding claims, wherein the systemically active drug is soluble in the said wall material.

14. A bandage as claimed in any one of the preceding claims wherein the pressure-sensitive adhesive is permeable to passage of the systemically active drug.

15. A bandage as claimed in any one of the preceding claims, wherein the drug is in solution in a pharmacologically acceptable solvent.

16. A bandage as claimed in any one of the preceding claims, wherein said wall material is a silicone rubber.

17. A bandage as claimed in any one of Claims 1 to 15 wherein said wall material is a hydrophilic polymer of an ester of an olefinic acid.

18. A bandage as claimed in any one of the preceding claims, wherein the pressure-sensitive adhesive is adapted to provide a liquid tight adhesive seal between the skin or mucosa and the bandage.

19. A bandage as claimed in any one of the preceding claims, wherein the pressure-sensitive adhesive is covered with a release member impervious to the drug.

20. A bandage as claimed in any one of Claims 1 to 18 wherein the outer surface of the backing member is coated with a material of low adhesion for the pressure-sensitive adhesive so that the bandage can be rolled about itself.

21. A bandage as claimed in Claim 1 and substantially as described in any one of the specific examples hereinbefore set forth.

22. A bandage as claimed in Claim 1 and substantially as herein described with reference to and as illustrated in Figures 1 and 2, 3 and 4 and 5 of the accompanying drawings.

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London, WC2A 1JQ.

Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to Patent No. 998,794.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon), Ltd.—1974.
Published at The Patent Office, 25 Southampton Buildings, London. WC2A 1AY,
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1361289 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

FIG. 1

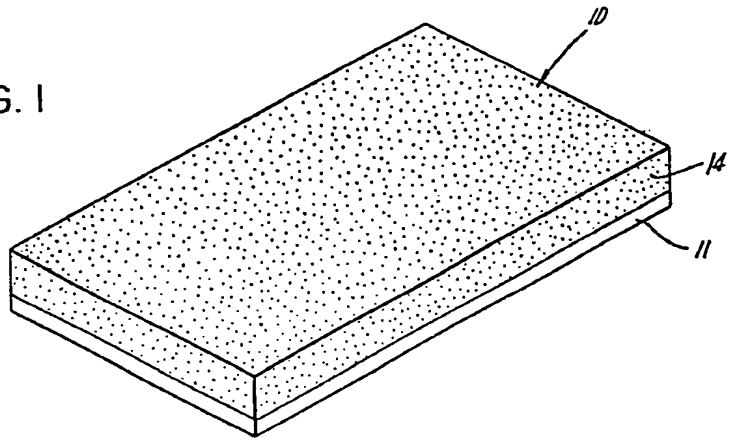

FIG. 2

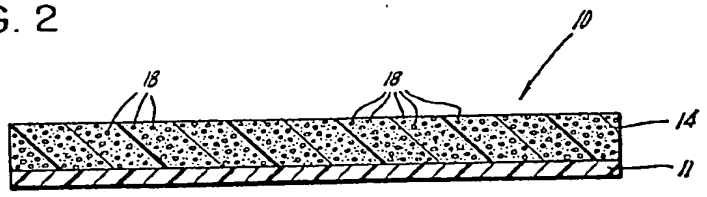

FIG. 3

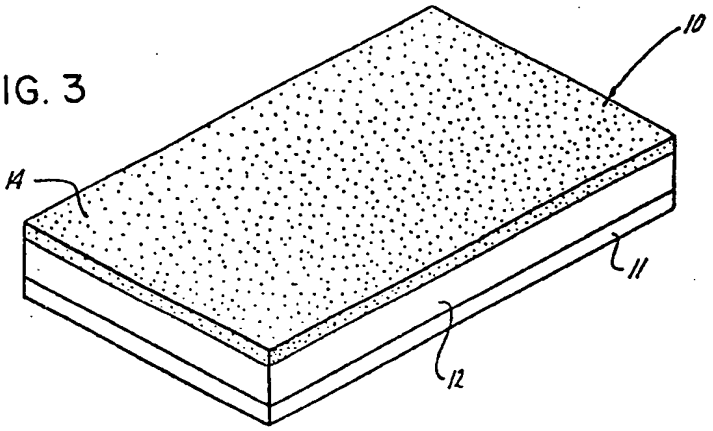

FIG. 4

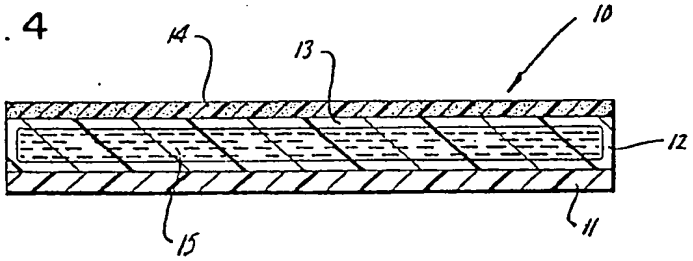

FIG. 5